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Use of Pamidronate in the Management of Acute Cancer-Related Hypercalcemia in Children

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Purpose. To determine whether pamidronate is a safe and effective agent for the treatment of severe hypercalcemia of malignancy in children.

Materials and Methods. A retrospective review of the charts of five children treated with pamidronate 1–2 mg/kg for severe, refractory hypercalcemia of malignancy. All children failed conventional therapy. Statistical analysis was done utilizing the two-tailed Student's t-test.

Results. All five children had complete resolution of their hypercalcemia in a predictable pattern within 24–48 hours. The average decrease in serum calcium was 1.63 mmol/L(6.54 mg/dl). ($P < .01$) The adverse effects were mild and transient, and consisted of hypocalcemia, hypophosphatemia, and hypomagnesemia.

Conclusions. Pamidronate at a dose of 1 mg/kg is a safe and effective treatment for severe, refractory hypercalcemia of malignancy in children. Med. Pediatr. Oncol. 30:117–121, 1998.

Key words: hypercalcemia; pamidronate

INTRODUCTION

Hypercalcemia is one of the metabolic complications of childhood malignancies. The incidence in children according to McKay and Furman's 29 year retrospective study is 0.4% [1]. The incidence within each category varies greatly in reported series [2]. Hypercalcemia is defined as serum calcium concentration greater than 3.24 mmol/L (13 mg/dl), a level usually associated with symptoms of hypercalcemia. The symptoms are generally non-specific and include generalized weakness, lethargy, nausea, vomiting, constipation, abdominal pain, and polyuria [3]. Left untreated, hypercalcemia can progress to stupor and coma, which in children has been seen with levels greater than 3.74 mmol/L (15 mg/dl) [4].

The treatment of hypercalcemia in childhood malignancies is vital in preventing further morbidity. Various pharmacological agents have been used including forced diuresis with saline and furosemide, calcitonin, corticosteroids, and mithramycin. However, they have a high failure rate and a high recurrence rate [2]. Newer agents have been developed which are more effective. One of these is pamidronate which belongs to a class of drugs referred to as bisphosphonates. These agents are analogs of pyrophosphate, and bind to hydroxyapatite crystals and block osteoclast-mediated resorption. In addition to the above mechanism of action for bisphosphonates in general, pamidronate also reduces osteoclast viability [3]. It is thought that this mechanism is responsible for its greater efficacy and longer duration of action. The side effects of pamidronate include fever in 20% of patients, hypocalcemia, hypophosphatemia, and/or hypomagnesemia in about 10%, transient decrease in lymphocytes and infusion site reaction.

Pediatric experience with pamidronate is limited [5,6,7,8,9,10]. Boudailliez et al. [5] treated a 10-year-old boy with leukemia-associated hypercalcemia with 2 mg/kg and had an excellent response. Profumo et al. [6] successfully treated a 5-year-old boy with severe immobilization hypercalcemia following a liver transplant with 60 mg/m^2 of pamidronate. Successfully, McIntyre et al. [7] treated a 16-year-old with 30 mg of pamidronate for immobilization hypercalcemia following a motor vehicle accident. Liens et al. [8] used pamidronate 60 mg in treating fibrous dysplasia of bone in a 13-year-old. Jansson et al. [9] used pamidronate 30 mg to treat a 17-year-old with hypercalcemia associated with hyperparathyroidism. Samuel et al. [10] treated five adolescents ranging in age from 13–16 years with clinical skeletal manifestations of Gaucher's disease with oral pamidronate. We describe the use of pamidronate in the treatment of tumor-associated hypercalcemia. Five children with various malignancies were studied (Table I and Figure 1).

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TABLE I. Clinical Response to IV Pamidronate

Case	Age	Disease	Symptoms	Peak calcium before pamidronate	Calcium level after pamidronate	Time to clinical response	Time to normal serum calcium	Adverse effects
#1	2	Astrocytoma	lethargy, anorexia, vomiting, weakness	3.84 mmol/L (15.4 mg/dl)	2.25 mmol/L (9.0 mg/dl)	24 hours	7 days	none
#2	15	ALL	leg weakness, vomiting, dry skin, anorexia	4.1 mmol/L (16.4 mg/dl)	1.52 mmol/L (6.1 mg/dl)	48 hours	6 days	hypocalcemia, hypophosphatemia
#3	9	ALL	none	3.79 mmol/L (15.2 mg/dl)	1.82 mmol/L (7.3 mg/dl)	16 hours	3 days	hypophosphatemia
#4	11	[a]DRCT	none	3.02 mmol/L (12.1 mg/dl)	1.89 mmol/L (7.6 mg/dl)	24 hours	8 days	hypocalcemia, hypomagnesemia, hyperphosphatemia
#5	4	[b]ARS	none	3.39 mmol/L (13.6 mg/dl)	2.50 mmol/L (10.0 mg/dl)	48 hours	5 days	hypophosphatemia

[a]Desmoplastic Round Cell Tumor
[b]Alveolar Rhabdomyosarcoma

MATERIALS AND METHODS

We retrospectively reviewed the charts of five patients who were treated with pamidronate for severe, refractory hypercalcemia of malignancy. Each child had failed standard therapy, consisting of furosemide and intravenous saline at twice the maintenance rate (forced diuresis), and was treated with pamidronate after obtaining informed consent from the parents. Statistical analysis of the change in serum calcium following treatment was performed utilizing the two-tailed Student's t-test.

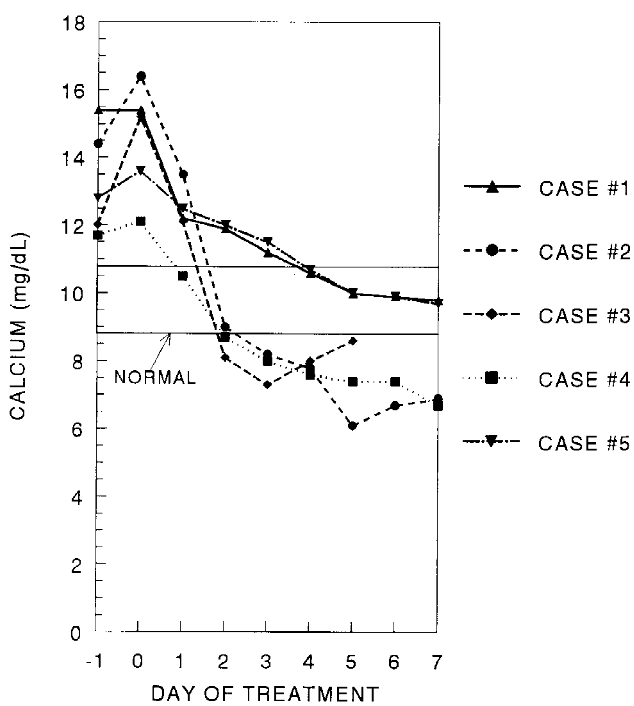

Fig. 1. The response of serum calcium in five children with severe hypercalcemia of malignancy unresponsive to standard therapy. Each child received pamidronate as an IV infusion once on day 0. Cases #1 and #4 received 2 mg/kg and cases #2, 3, and 5 received 1 mg/kg. Cases #1, #2, and #4 received a 24-hour infusion ending on day 1. Cases #3 and #5 received a 4 and 3-hour infusion respectively on day 0.

RESULTS

Case #1

This is a 2-year-old female with a diagnosis of astrocytoma, status post autologous bone marrow transplant who was admitted with a four day history of lethargy, anorexia, vomiting, weakness, and pain in her legs. She was not receiving any therapy for her malignancy at this time. On the day of admission, she was found to have a serum calcium of 3.22 mmol/L (12.9 mg/dl). [normal 2.17–2.67 mmol/L (8.7–10.7 mg/dl)]. An intact PTH level was 12 ng/L (normal 10–65 ng/L), and a 25-(OH) vitamin D was 12.5 nmol/L (normal 45–90 nmol/L). Her serum ionized calcium was 2.28 mmol/L (normal 1.2–1.38 mmol/L). She was treated initially with an intravenous (IV) infusion of saline at twice the maintenance rate and furosemide 1 mg/kg every six hours to no avail. Her serum calcium rose to 3.84 mmol/L (15.4 mg/dl) and the serum ionized calcium rose to 2.42 mmol/L. The remainder of her electrolytes and minerals were within normal limits. At this time she was given two doses of etidronate 7.5 mg/kg IV each dose over three hours, however 48 hours after the etidronate was given, her serum calcium was 3.84 mmol/L (15.4 mg/dl) and the ionized calcium was 2.32 mmol/L, still far above the normal range, and the patient remained symptomatic. She was then given pamidronate 40 mg IV (2 mg/kg) over 24 hours. Twenty-four hours after completion of the infusion, the serum calcium was 3.04 mmol/L (12.2 mg/dl) and the ionized calcium was 1.99 mmol/L. Over the next week, the serum calcium decreased to a level of 2.44 mmol/L (9.8 mg/dl). The ionized calcium remained elevated, but was

significantly lower at 1.45 mmol/L and the patient reported resolution of her symptoms and was discharged. Three weeks following completion of the pamidronate, the serum calcium was 2.25 mmol/L (9.0 mg/dl) and the ionized calcium was 1.28 mmol/L. This patient experienced no side effects or complications from her treatment.

Case #2

This is a 15-year-old female with a diagnosis of acute lymphoblastic leukemia, status post allogeneic bone marrow transplant who complained of malaise, leg weakness, vomiting, anorexia, and dry skin. Her leukemia was in remission at this time (though she subsequently relapsed), and she was not receiving any chemotherapy. On the day of admission, she was found to have a serum calcium of 3.59 mmol/L (14.4 mg/dl) and an ionized calcium of 2.10 mmol/L. An intact PTH level was 2 ng/L, a 25-(OH) vitamin D level was <10 nmol/L, and a PTHrp was 5 pmol/L (normal <2 pmol/L). She was initially treated with forced diuresis in the same manner as the previous case, however her serum calcium continued to increase and reached 4.09 mmol/L (16.4 mg/dl). She was then given pamidronate 40 mg IV (1 mg/kg) over 24 hours. Twenty-four hours after completion of the dose, the serum calcium decreased to 3.37 mmol/L (13.5 mg/dl) with an ionized calcium of 1.67 mmol/L, and at 48 hours her serum calcium normalized at 2.25 mmol/L (9.0 mg/dl) and 1.34 mmol/L, respectively. However, her serum inorganic phosphorus was 0.45 mmol/L (1.4 mg/dl) [normal 0.87–1.45 mmol/L (2.7–4.5 mg/dl)], which necessitated treatment with supplemental phosphate. The patient's symptoms of hypercalcemia completely resolved within 48 hours of therapy. As with the previous patient, the serum calcium continued to decrease during the week following treatment and reached a nadir of 1.52 mmol/L (6.1 mg/dl) and an ionized calcium of 0.93 mmol/L. Her only complaint at this time was abdominal pain. Other signs of hypocalcemia were not evident. She was treated at first with IV calcium gluconate and responded well with normalization of her ionized calcium to 1.17 mmol/L within 24 hours. This patient was then discharged on oral calcium supplementation which was required for two weeks.

Case #3

This is a 9-year-old female with relapsed B cell acute lymphoblastic leukemia. Upon admission, she was found to have a serum calcium of 2.99 mmol/L (12 mg/dl). Re-induction chemotherapy was instituted which led to remission. She was initially treated for the hypercalcemia with forced diuresis as in the two previous cases, however, her serum calcium continued to rise and reached 3.79 mmol/L (15.2 mg/dl). At this time she was treated with pamidronate 60 mg IV (2 mg/kg) over 4 hours. Sixteen hours after completion of the dose, her serum calcium was 3.02 mmol/L (12.1 mg/dl). Her calcium continued to fall reaching a nadir on the third day of treatment of 1.82 mmol/L (7.3 mg/dl) with an ionized calcium of 0.94 mmol/L. Her serum phosphorus was 0.52 mmol/L (1.6 mg/dl) necessitating treatment with supplemental phosphate. She experienced no symptoms of hypocalcemia. She achieved eucalcemia within two days and required no further therapy.

Case #4

This is an 11-year-old male with end stage desmoplastic round cell tumor with bone metastases receiving palliative care. On routine screening, he was found to have a serum calcium of 3.02 mmol/L (12.1 mg/dl) with an ionized calcium of 1.60 mmol/L. He also had anorexia and generalized weakness. He was initially treated with forced diuresis as in the previous cases, but failed to respond, and was then given pamidronate 60 mg IV (2 mg/kg) over 24 hours. His serum calcium was 2.62 mmol/L (10.5 mg/dl) 24 hours after completion of the dose and 8.0 mg/dl with an ionized calcium of 1.13 mmol/L on the third day. His serum calcium also continued to fall until it reached a nadir on the fifth day of 1.85 mmol/L (7.4 mg/dl) with an ionized calcium of 0.99 mmol/L. At this time he had tetany. He was given a bolus of calcium gluconate which alleviated the symptoms and increased the serum calcium to 1.32 mmol/L. Following this episode, his serum calcium fell again to 1.67 mmol/L (6.7 mg/dl) with an ionized calcium of 1.00 mmol/L, but no further signs or symptoms of hypocalcemia were evident. The patient required supplementation with IV calcium gluconate. Additionally, he developed the complication of hyperphosphatemia [2.81 mmol/L (8.7 mg/dl)] and hypomagnesemia [0.41 mmol/L (1.0 mg/dl)]. [normal 0.62–1.03 mmol/L (1.5–2.5 mg/dl)]. The hyperphosphatemia resolved spontaneously, however, the hypomagnesemia required supplemental therapy with magnesium.

Case #5

This is a 4-year-old female with relapsed alveolar rhabdomyosarcoma receiving palliative care. On routine screening as an inpatient she was found to have a serum calcium of 3.19 mmol/L (12.8 mg/dl). She did not have any symptoms specifically referable to the hypercalcemia. She was initially treated with forced diuresis as in the previous cases, but failed to respond. Her serum calcium increased to 3.39 mmol/L (13.6 mg/dl) with an ionized calcium of 1.91 mmol/L. She was then given pamidronate 20 mg IV (1 mg/kg) over three hours. Twenty-four hours following the dose, her serum calcium decreased to 3.12 mmol/L (12.5 mg/dl). At 48 hours, the serum calcium was 2.99 mmol/L (12.0 mg/dl) with an ionized calcium of 1.71 mmol/L. By the fifth

day, her serum calcium was 2.50 mmol/L (10.0 mg/dl) and remained stable. She developed hypophosphatemia at 24 hours following the dose of pamidronate to 0.58 mmol/L (1.8 mg/dl) and was treated. She suffered no other adverse effects.

The average serum calcium prior to instituting treatment with pamidronate for the five cases was 3.63 mmol/L (14.5 mg/dl). On day 7 following treatment, the average serum calcium was 2.0 mmol/L (8.0 mg/dl). Thus, the average decrease in serum calcium was 1.63 mmol/L (6.54 mg/dl). ($p < .01$)

DISCUSSION

Hypercalcemia of malignancy is a relatively uncommon occurrence in pediatric oncology, however untreated can lead to serious consequences. Two of our patients had a partial diagnostic evaluation, and both demonstrated low levels of PTH and 25-(OH) vitamin D. One patient was tested for PTHrp, and her level was elevated. Thus, for these two patients, excessive bone resorption secondary to malignancy is the likely cause, whereas for the other three patients, the cause can not be proven, but is believed to be the same. The most effective therapy is treatment of the underlying malignancy, however, in many cases, hypercalcemia occurs during end-stage disease. Symptomatic treatment has relied on forced diuresis with saline and furosemide or corticosteroids, but results have been disappointing. Pamidronate offers a safe and effective therapy for this condition. We treated five patients, all of whom failed treatment for their underlying disease and developed hypercalcemia of malignancy with pamidronate after they failed conventional treatment for hypercalcemia. Only case #3 was receiving concomitant chemotherapy. We therefore conclude that the excellent response seen in 4 of the 5 patients was due solely to the pamidronate, while in the other patient, the effect of the pamidronate is confounded by her chemotherapy. We believe however, that the pamidronate played a vital role, as the timing of her response was similar to that of the other patients, although this cannot be proven. None of the patients suffered severe adverse effects, and the transient mineral disturbances attributed to the treatment were easily reversed. In addition, none of the patients had recurrences of hypercalcemia. It is, however, unclear whether or not this could be attributed to pamidronate.

Several clinical trials of pamidronate for the treatment of hypercalcemia in adults have proven its effectiveness. Ralston et al. [11] compared pamidronate with mithramycin and corticosteroids plus calcitonin and showed that the fall in serum calcium with pamidronate was slower but more progressive, and long-term control of hypercalcemia was superior. Thiebaud et al. [12] compared four doses of pamidronate in 52 adults with hypercalcemia of malignancy, and found that higher doses (60 mg and 90 mg) were more effective than lower doses. Nussbaum et al. [13] also showed that larger doses were more effective. Gucalp et al. [14] compared pamidronate with etidronate in a double-blind randomized study, and found pamidronate to be more effective. Gurney et al. [15] studied PTHrp as a marker for responsiveness to pamidronate and found a direct correlation between diminution of PTHrp levels and serum calcium levels following treatment with pamidronate.

At this point, experience with pamidronate in pediatrics has been limited only to several case reports [5,6,7,8,9,10]. Herein we describe the effectiveness of pamidronate in the treatment of five children with hypercalcemia who were refractory to the initial standard therapy. The doses ranged from 1–2 mg/kg, and were chosen based upon the prior experience, and each patient's severity of hypercalcemia and the presence of bone metastases. All five patients had an excellent response to treatment with few complications which were treatable. None of our patients had fever during the infusion, nor did any have local infusion site reactions since all were infused via central venous access devices. Three out of five patients suffered transient hypocalcemia of which two required replacement therapy and one became symptomatic. Two patients had transient hypophosphatemia requiring replacement therapy, and one had transient hyperphosphatemia which resolved without treatment. One patient had transient hypomagnesemia which required replacement therapy. Thus, pamidronate frequently caused metabolic derangements, however they were transient, easily correctable, and with one exception asymptomatic.

Case #1 had the most severe symptoms and the highest levels of serum calcium and received a dose of 2 mg/kg and had slow, but complete resolution with no adverse reactions. This patient received etidronate prior to therapy with pamidronate. Since she had no response for 48 hours following the etidronate, sufficient time for a response [14], we believe it was ineffective. The patient in case #4 also received 2 mg/kg and subsequently developed hypocalcemic tetany. The other three patients received a dose of 1 mg/kg and had good responses with only mild transient hypocalcemia and hypophosphatemia. Thus, the proper dose of pamidronate in children is probably in the range of 1–2 mg/kg. In an early study of pamidronate in adults with hypercalcemia of malignancy, Body et al. [15] determined that the proper dose is 0.25–1.5 mg/kg for adults. None of our patients required a repeated dose of pamidronate, but it may be given again for subsequent episodes of hypercalcemia.

CONCLUSIONS

In conclusion, we believe that pamidronate is an effective agent for the treatment of hypercalcemia associ-

ated with childhood malignancies. At this time, we recommend a starting dose of 1 mg/kg, although it seems likely that some patients may require an additional 1 mg/kg. Further clinical experience will be necessary to establish its efficacy and optimal dose schedule, although a formal dose-finding study will be difficult to perform due to the rarity of the condition in children.

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